NOSCM™
NEW ORLEANS SUMMER CANCER MEETING

July 14–16, 2023
The Roosevelt Hotel
New Orleans, Louisiana

Neoadjuvant and Adjuvant Treatment of Early Stage NSCLC

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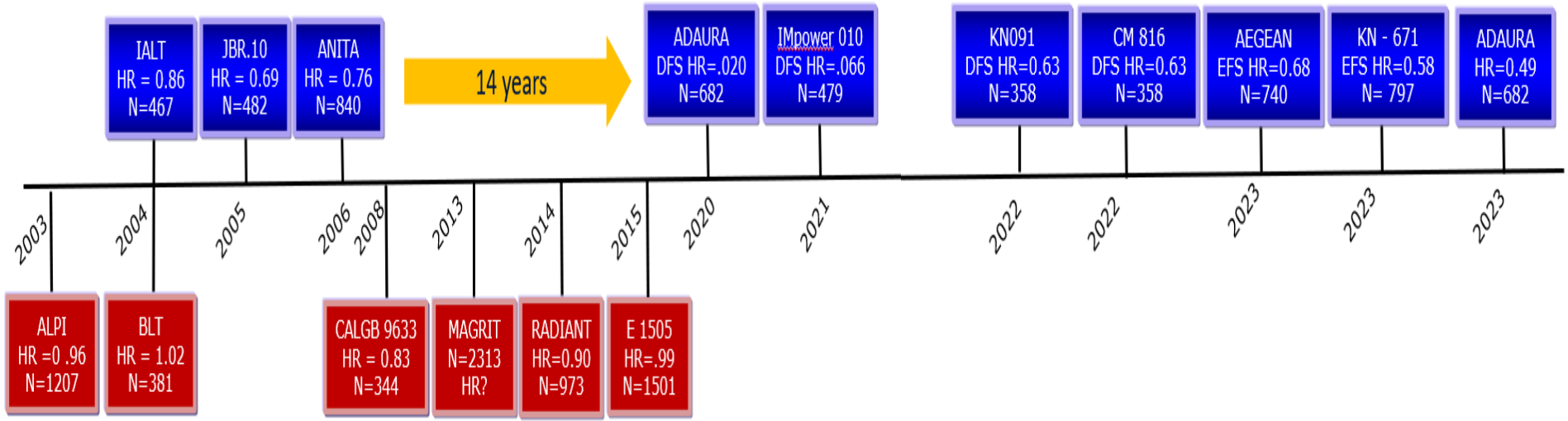
Major Systemic Treatment Advances in Early-Stage NSCLC

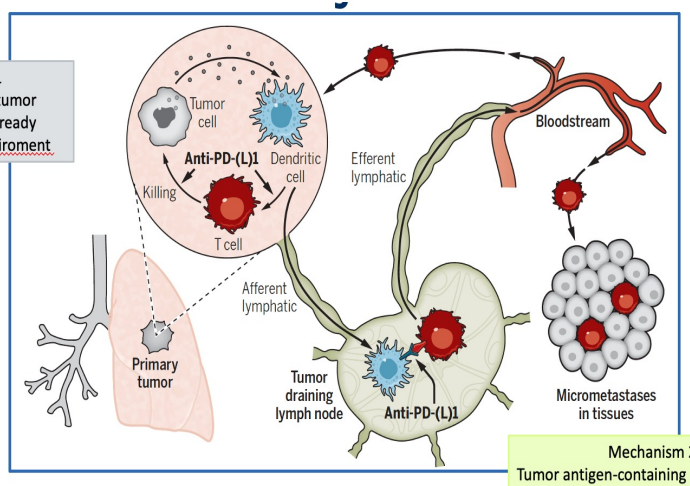
Phase III Trials



ALPI–Scagliotti GV et al. J Natl Cancer Inst 2003 ;BLT- Waller D et al. Eur J Cardiothorac Surg 2004; IALT–Arriagada R et al. N Engl J Med 2004; JBR.10–Winton T et al. N Engl J Med 2005; ANITA–Douilland JY et al. Lancet Oncol 2006; CALGB 9633–Strauss GM et al. J Clin Oncol 2008; RADIANT – Kelly K et al. J Clin Oncol 2014;MAGRIT-Vansteenkiste J et al. Lancet Oncol 2016; EGOG 1505 Wakelee HA et l Lancet Oncol 2017; ADAURA-Herbst R et al. N Engl J Med 2021; IMpower 010 -Felip E et al. Lancet Oncol 2021; PEARLS- Paz-Ares L et al. ESMO 2022; CheckMate 816- Forde P et al. N Engl J Med 2022;

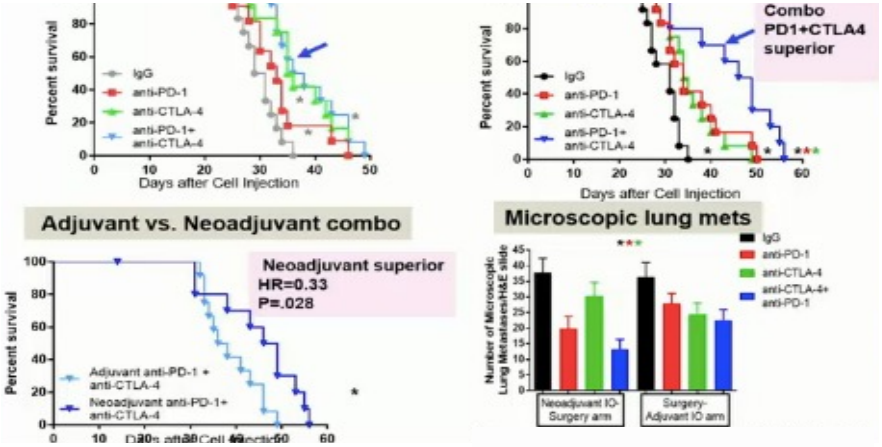
Mechanisms of enhancing a systemic immune response with neoadjuvant ICP inhibitors

Mechanism 1
"in situ" expansion of tumor
Specific T cell clones already
In the tumor microenviroment



Mechanism 2
Tumor antigen-containing dendritic cells in the tumor traffic to the tumo draining lymph nodes to enhance production of tumor-specific T cells

Adjuvant vs neoadjuvant immunotherapy in murine models of lung adenocarcinoma



- Anti-PD-1/PD-L1 therapy requires the interaction between tumor cells, T cells and antigen presenting cells
- Higher probability that these interactions will occur in an established macroscopic tumor versus a microscopic tumor that requires time to recruit immune cells and establish a microenvironment.

Topilian SL, et al. Science Jan 2020

Cascone T et al, AACR 2018 poster, abstr 1719

Early Clinical Data in Support for Neoadjuvant Immune Checkpoint Inhibitors

Trial	Stage	N	Regimen	Squamous	Non-Squamous	Surgery	TRAE	ORR	MPR	pCR
Forde	IB-IIIA	21	Nivolumab	29%	62%	95%	4.5%	10%	45%	15%
MK3475-223	I-II	15	Pembrolizumab	46%	46%	87%	NR	NR	31%	15%
LCMC3	IB-IIIB	101	Atezolizumab	35%	65%	89%	6%	7%	19%	5%
NEOSTAR®	I-IIIA (N2 single)	23	Nivolumab	43%	57%	96%	13%	22%	17%	9%
		21	Nivolumab Ipilimumab	33%	62%	81%	23%	19%	33%	29%
Gao	IA-IIIA	40	Sintilimab	83%	15%	93%	10%	20%	41%	16%
NADIM	IIIA (N2 or T4)	46	Nivolumab Chemotherapy	35%	61%	89%	NR	74%	83%	59%
Shu	IB-IIIA	30	Atezolizumab Chemotherapy	40%	57%	87%	6%	63%	57%	33%
Zinner	IB-IIIA	13	Nivolumab Chemotherapy	69%	31%	100%	NR	46%	77%	31%
SAKK 16/14	IIIA (N2)	67	Chemotherapy followed by Durvalumab	33%	55%	85%	NR	58%	60%	18%

Neoadjuvant Phase III Trials- Trial Characteristics

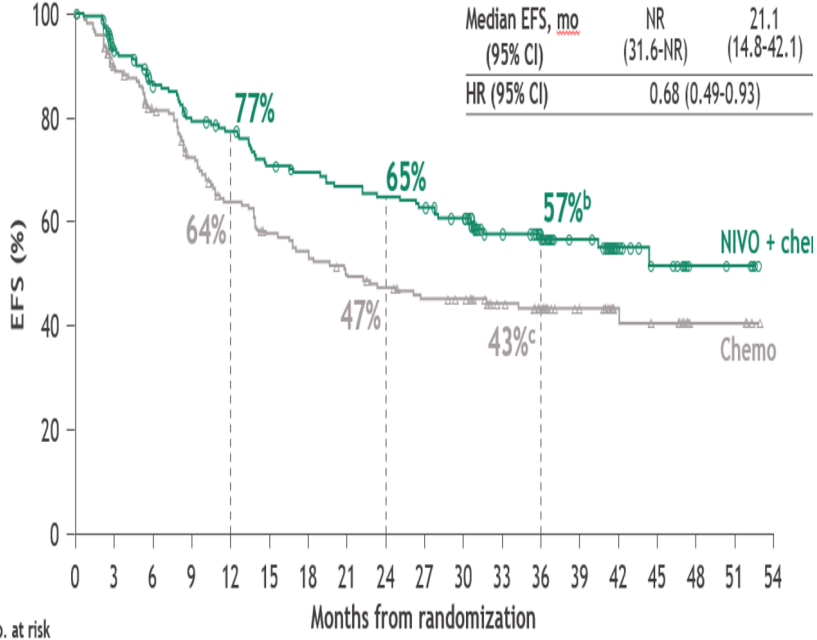
Study	N	Stage	PD-L Testing requirement Stratification	Primary Endpoint	Allowance of EGFR or ALK + tumors	Comments
CHECKMATE 816 (NCT02998528) [Forde NEJM 2022]	505	Resectable stage IB (≥4 cm) to IIIA (AJCC 7th edition)	Required Stratification: <1% vs ≥1%	EFS pCR	Excluded	No adjuvant therapy
PERIOPERATIVE TREATMENT						
AEGEAN (NCT03800134]	825	Resectable stage II/III (AJCC 8th edition)	Required Stratification: <1% vs ≥1%	EFS pCR	Originally included but later excluded per protocol revision	Adjuvant durvalumab q 4 wks x 12 cycles
KEYNOTE-671 (NCT03425643]	786	Resectable stage II, IIIA, and IIIB (T3-4N2) (AJCC 8th edition)	Required Stratification: <50% vs >50%	EFS OS	Allowed	Adj pembrolizumab q 3wks x 13 cycles
NEOTORCH (JS001-029-III-NSCLC) (NCT04158440)	500	Resectable stage II or stage III disease. (TNM edition ?)	Required Stratification: <1% vs ≥1%	EFS (stage III) EFS (stage II-III) MPR (stage III) MPR (stage II-III)	Excluded	1 cycle chemo + toripalimab post surgery then toripalimab X 13 cycles
BGB-A317-315 (NCT04379635]	380	Resectable stage II, IIIA (AJCC edition not reported)	Required Stratification: <1% vs >1%	MPR EFS	Excluded	Pending results
IMpower 030 (NCT03456063]	453	Resectable stage II, IIIA, and select IIIB (AJCC 8th edition)	Collected but not used	EFS	Excluded	Pending results Adj Atezolizumab x16 cycles
CA209-77T (NCT04025879]	452	Resectable stage II-IIIB (AJCC 8th edition)	Not reported	EFS	Excluded	Pending results
Rationale 315	450	Resectable stage II-IIIA TNM edition ?	PD-L1 (≥1% vs <1%)	EFS	Excluded	Pending results Tislelizumab 200 mg (Neoadj 3-4 cycles) Adj 400 mg q 6 weeks x 8

Primary endpoints: EFS and/or pathological complete response rate

Neoadjuvant Regimen
Check-Mate 816 – 3 Year Update

Median FU
41.4 M

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	

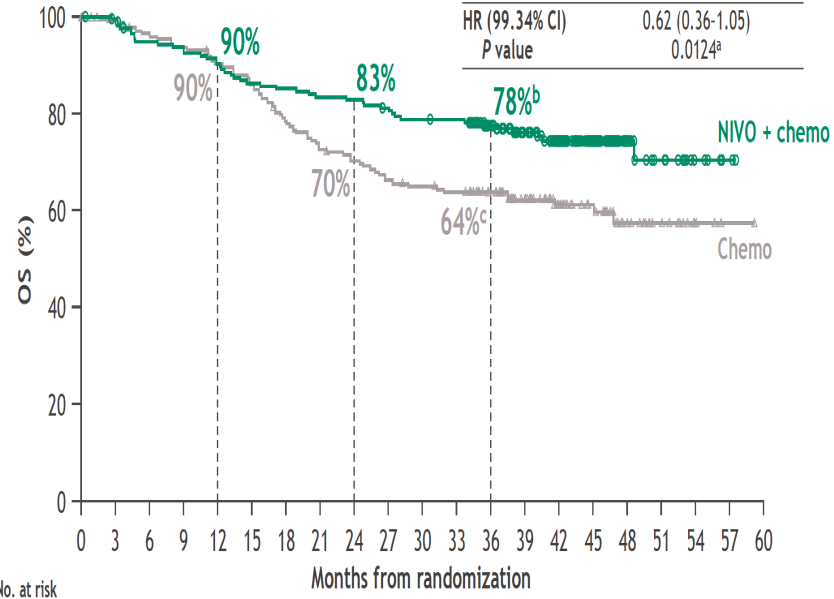


No. at risk

NIVO + chemo	179	152	136	125	119	108	104	100	97	94	88	69	57	38	20	13	6	5	0
Chemo	179	146	128	110	95	84	79	72	67	62	60	48	39	27	15	13	4	4	0

HR = 0.63 at first report

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo (95% CI)	NR (NR-NR)	NR (46.8-NR)
HR (99.34% CI)	0.62 (0.36-1.05)	
P value	0.0124[a]	



No. at risk

NIVO + chemo	179	176	166	163	158	151	149	146	145	141	137	136	117	95	67	44	23	14	6	2	0
Chemo	179	173	166	162	155	149	134	124	119	112	109	106	95	75	52	38	22	14	4	1	0

ELCC 2023

Perioperative Regimen - EFS

AEGEAN

EFS using RECIST v1.1 (BICR) (mITT)

First planned interim analysis of EFS

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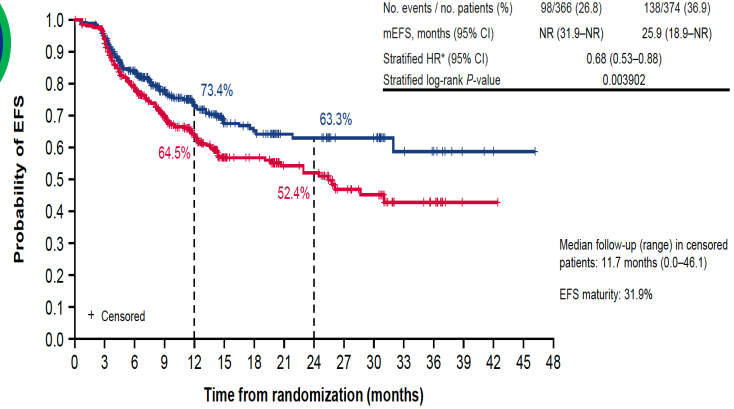
Median FU 11.7 M

	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	



Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

No. at risk:

D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

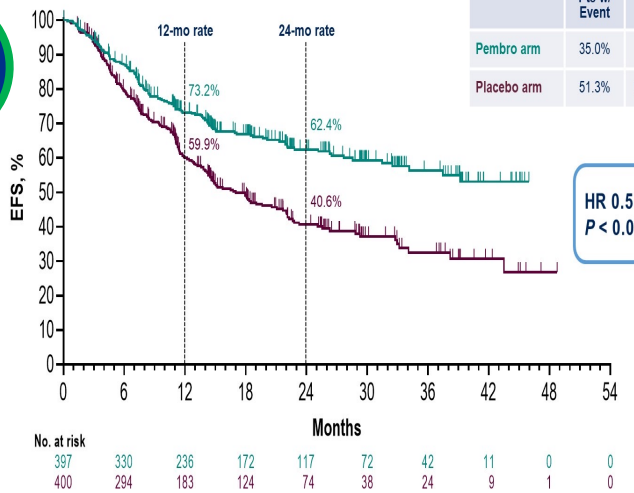
DCO = Nov 10, 2022. EFS is defined as time from randomization to the earliest of: (A) progressive disease (PD) that precludes surgery, (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery, (C) local/distant recurrence using BICR 10.00 x 5.62 in 1, or (D) death from any cause. *HR <1 favors the D arm versus the PBO arm. Median and landmark estimates calculated using the Kaplan–Meier method; HR calculated using a stratified Cox proportional hazards model; and *P*-value calculated using a stratified log rank m factors: disease stage (II vs III) and PD-L1 expression status (<1% vs ≥1%). Significance boundary = 0.009899 (based on total 5% alpha), calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary. mEFS, median EFS; NR, not reached.

KEYNOTE 671

Event-Free Survival

Median FU 25.2M

	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)



HR 0.58 (95% CI, 0.46-0.72)
P < 0.00001

No. at risk

397	330	236	172	117	72	42	11	0	0
400	294	183	124	74	38	24	9	1	0

EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

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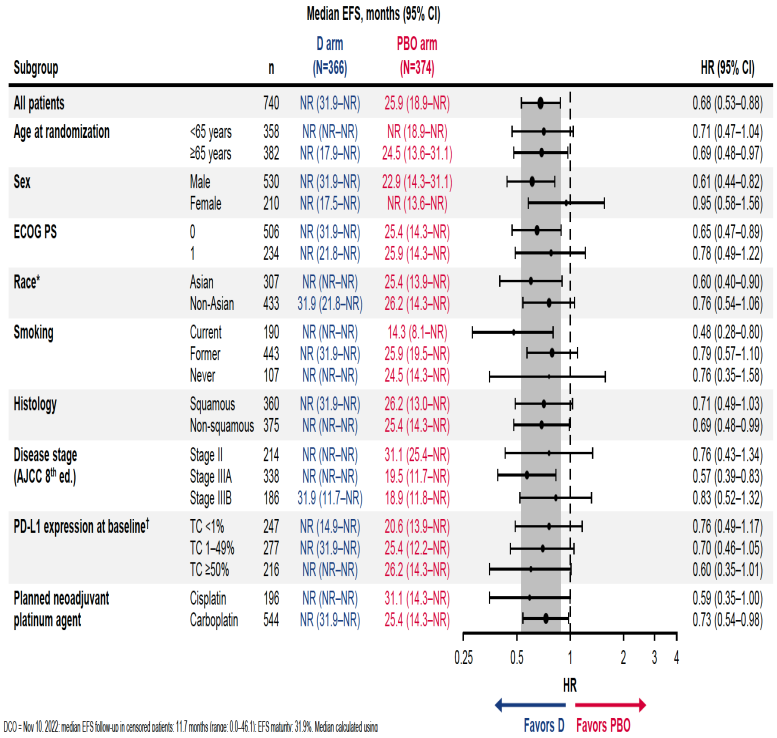
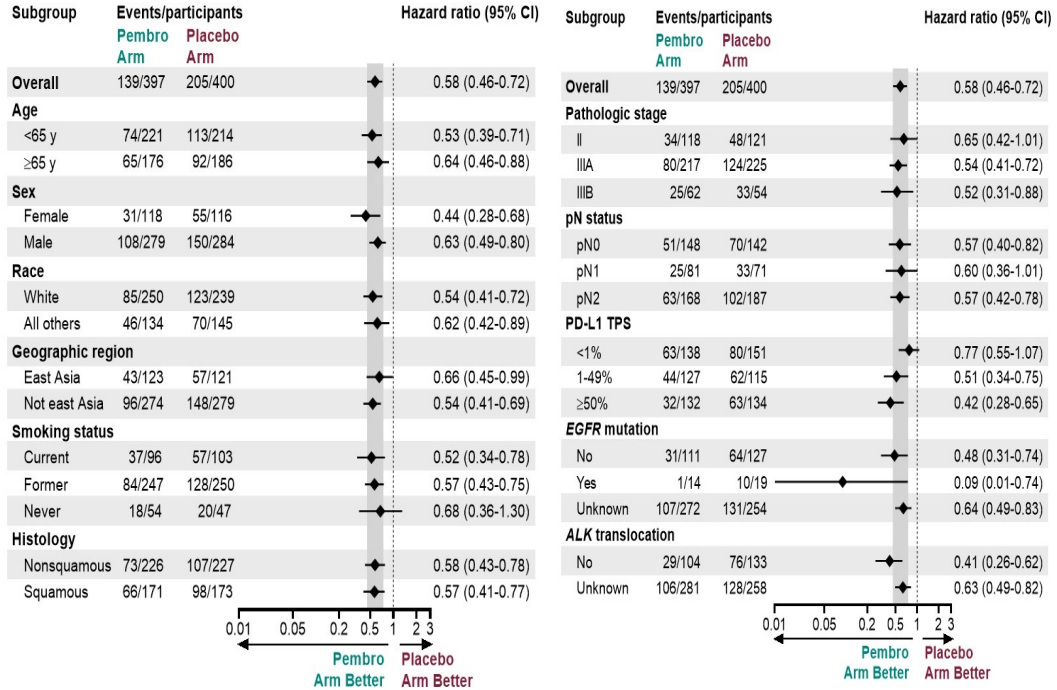
Perioperative Regimen – EFS By Subgroups

AEGEAN



DCO = Nov 10, 2022; median EFS follow-up in censored patients: 11.7 months (range: 0.0–46.1); EFS maturity: 31.9%. Median calculated using

KEYNOTE 671



Perioperative Regimen – Pathological Response

AEGEAN

Pathologic response per IASLC 2020 methodology* (mITT)
Final analysis

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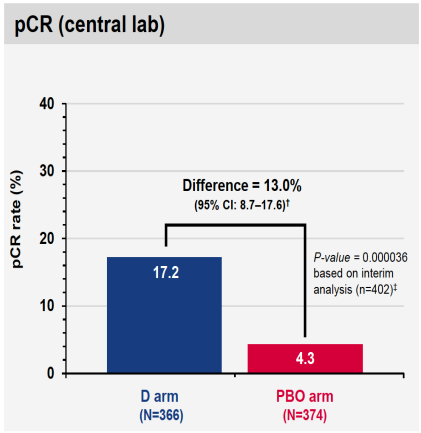
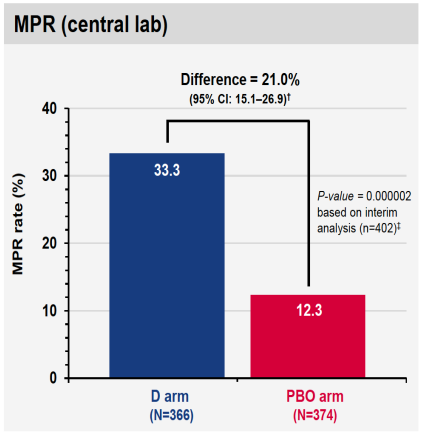
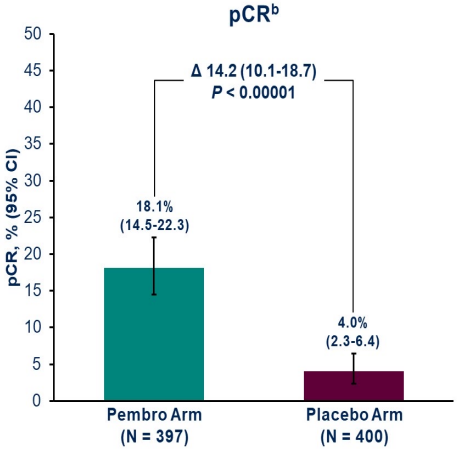


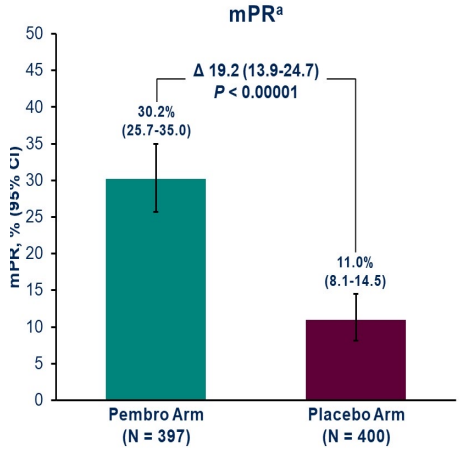


*Using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumor bed (Travis WD, et al. *J Thorac Oncol* 2020;15:709-40). pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR = less than or equal to 10% viable tumor cells in lung primary tumor after complete evaluation of the resected lung cancer specimen. To be eligible for pathologic assessment, patients needed to have received three cycles of neoadjuvant study Tx per protocol. Patients who were not evaluable were classified as non-responders. †CIs calculated by stratified Miettinen and Nurminen method. ‡No formal statistical testing was performed at the pCR final analysis (DCO: Nov 10, 2022; n=740 [data shown]). Statistical significance was achieved at the interim pCR analysis (DCO: Jan 14, 2022; n=402; *P*-value for pCR/MPR calculated using a stratified Cochran-Mantel-Haenszel test with a significance boundary = 0.000082 calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary).

KEYNOTE 671

Pathological Response
Assessed per Blinded, Independent Pathologist Review





[a] Per IASLC criteria, defined as ≤10% viable tumor cells in resected primary tumor and lymph nodes. [b] Per IASLC criteria, defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). Data cutoff date for IA1: July 29, 2022.

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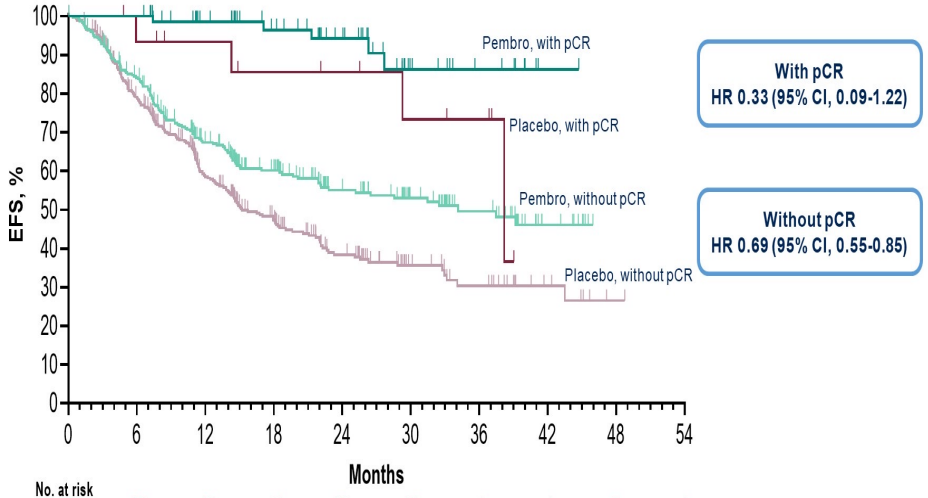
KEYNOTE 671 - Pathological Response

Exploratory Analysis of EFS by pCR Status

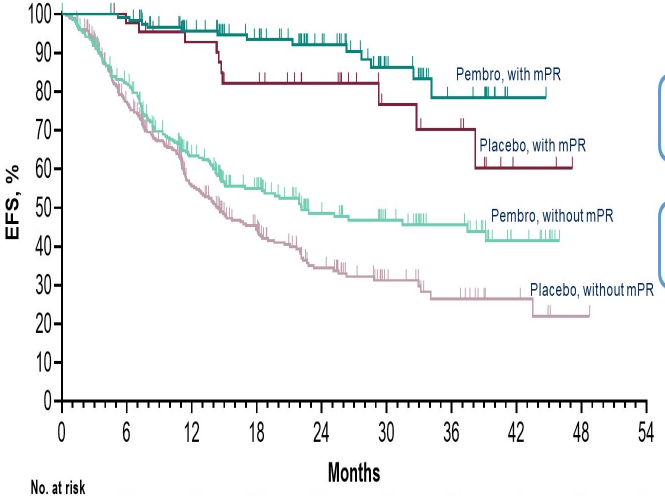


With pCR
HR 0.33 (95% CI, 0.09-1.22)

Without pCR
HR 0.69 (95% CI, 0.55-0.85)

pCR defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022.

Exploratory Analysis of EFS by mPR Status



With mPR
HR 0.54 (95% CI, 0.24-1.22)

Without mPR
HR 0.73 (95% CI, 0.58-0.92)

defined as ≤10% viable tumor cells in resected primary tumor and lymph nodes. EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, ectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022.

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Perioperative Regimen – Adverse Events

AEGEAN

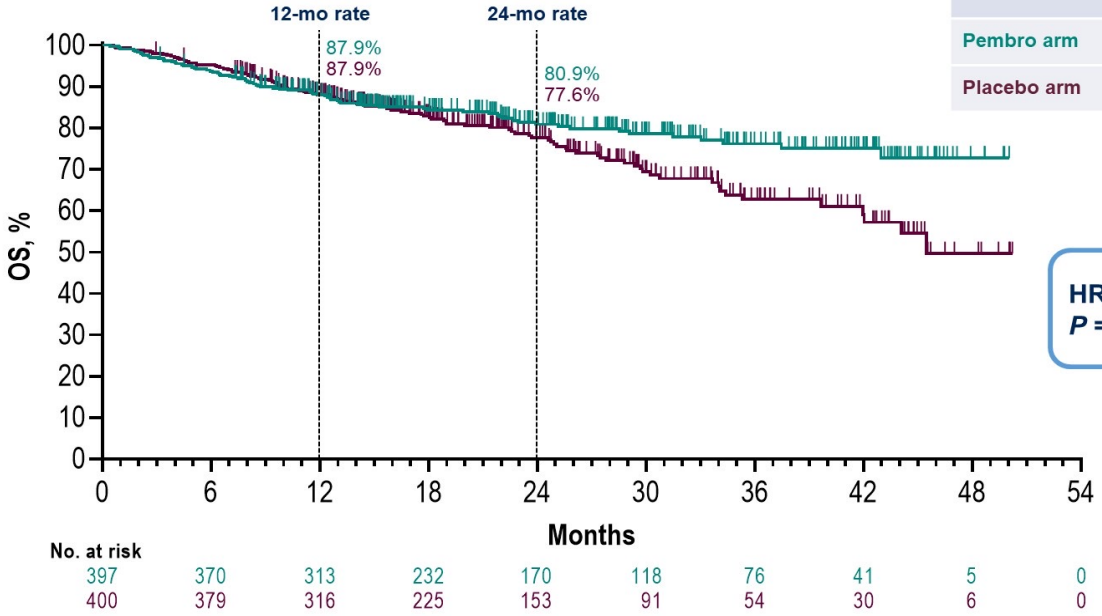
Overall study period (inclusive of the neoadjuvant, surgical, and adjuvant Tx phases)†	D arm (N=400)	PBO arm (N=399)
Any-grade all-causality AEs, n (%)	386 (96.5)	378 (94.7)
Max. grade 3 or 4	169 (42.3)	173 (43.4)
SAE	150 (37.5)	126 (31.6)
Outcome of death	23 (5.8)	15 (3.8)
Leading to discontinuation of D / PBO	48 (12.0)	24 (6.0)
Leading to cancellation of surgery	7 (1.8)	4 (1.0)
Any-grade AEs possibly related to D / PBO / CT, n (%)	346 (86.5)	322 (80.7)
Max. grade 3 or 4	129 (32.3)	132 (33.1)
Outcome of death‡	7 (1.8)	2 (0.5)
Any-grade immune-mediated AEs§, n (%)	94 (23.5)	39 (9.8)
Grade 3 or 4	16 (4.0)	10 (2.5)
Pneumonitis (any grade)¶	15 (3.8)	7 (1.8)

KEYNOTE 671

	Pembro Arm (n = 396)	Placebo Arm (n = 399)
Exposure		
Days on pembro or placebo, median (range)	332 days (1-567)	315 days (1-596)
No. pembro or placebo administrations, median (range)	12 (1-17)	10 (1-17)
Treatment-related AEs[a]	383 (96.7%)	379 (95.0%)
Grade 3-5	178 (44.9%)	149 (37.3%)
Serious	70 (17.7%)	57 (14.3%)
Led to death	4 (1.0%)[b]	3 (0.8%)[c]
Led to discontinuation of all study treatment	50 (12.6%)	21 (5.3%)
Immune-mediated AEs and infusion reactions	100 (25.3%)	42 (10.5%)
Grade 3-5	23 (5.8%)	6 (1.5%)
Serious	21 (5.3%)	6 (1.5%)
Led to death	1 (0.3%)[d]	0
Led to discontinuation of all study treatment	20 (5.1%)	3 (0.8%)

Managable AE profiles

KEYNOTE 671 – Overall Survival



	Pts w/ Event	Median (95% CI), mo
Pembro arm	19.1%	NR (NR-NR)
Placebo arm	25.3%	45.5 (42.0-NR)

HR 0.73 (95% CI, 0.54-0.99)
***P* = 0.02124[a]**

OS defined as time from randomization to death from any cause. [a] Significance boundary not met at IA1; OS will continue to be tested according to the analysis plan. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

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68 58 68

By the Numbers

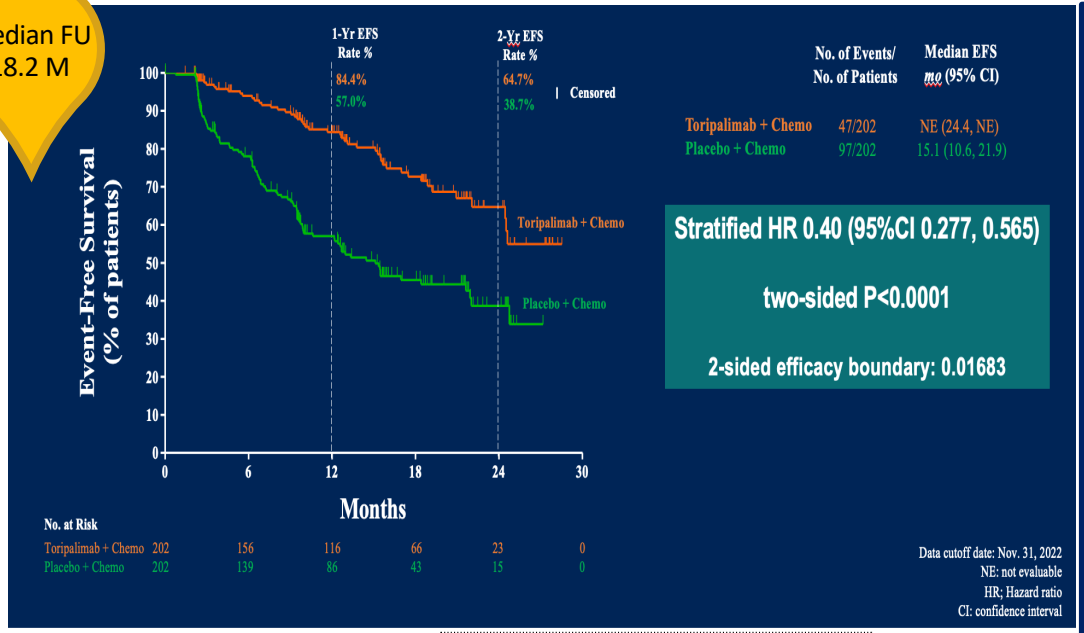
24 18 17

Trial	N	Follow Up	Stage III	PD-L1 ≥ 50% ≤ 1%	EFS HR (95% CI)	OS HR (95% CI)	Completed Neoadjuvant Tx	cPR	R0 Resection	Completed Adjuvant Tx
CM 816	358	41.4 months	66% (no IIIB) 7th ed	22% 43%	HR 0.68 (0.49-0.93)	HR 0.62 (0.36-1.05)	93.8%	24%	83.2%	NA
KN 671	797	25.2 months	70%	33% 36%	HR 0.58 (0.46-0.72)	HR 0.71 (0.54-0.99)	74.5%	18.1%	92%	40.4%*
AEGEAN	740	11.7 months	71%	29% 33%	HR 0.68 (0.53-0.88)	NR	84.7%	17.2%	94.7%	24.0%**

* Patients on treatment (11%)
** Patients on treatment (23%)

NEOTORCH (STAGE III) - EFS

Median FU
18.2 M



	No. of Events/ No. of Patients	Median EFS *mo* (95% CI)
Toripalimab + Chemo	47/202	NE (24.4, NE)
Placebo + Chemo	97/202	15.1 (10.6, 21.9)

Stratified HR 0.40 (95%CI 0.277, 0.565)

two-sided P<0.0001

2-sided efficacy boundary: 0.01683

Data cutoff date: Nov. 31, 2022
NE: not evaluable
HR; Hazard ratio
CI: confidence interval

Subgroups	Toripalimab + Chemo Events/Total	Placebo + Chemo Events/Total	Hazard Ratio (95% CI)
Disease Stage			
IIIA	34/136	65/136	0.44 (0.287, 0.661)
IIIB	13/65	31/64	0.30 (0.149, 0.559)
PD-L1 Expression			
TC>=1%	28/133	65/132	0.31 (0.197, 0.481)
TC<1% or Not Evaluable	19/69	32/70	0.59 (0.327, 1.034)
Pathological Type			
Non-squamous Cell Carcinoma	12/45	21/45	0.54 (0.257, 1.079)
Squamous Cell Carcinoma	35/157	76/157	0.35 (0.234, 0.523)
Age			
<65	33/140	66/138	0.41 (0.267, 0.618)
>=65	14/62	31/64	0.34 (0.177, 0.635)
Sex			
Male	42/181	91/189	0.38 (0.259, 0.541)
Female	5/21	6/13	0.54 (0.154, 1.796)
ECOG			
0	20/70	38/73	0.44 (0.249, 0.743)
1	27/132	59/129	0.36 (0.226, 0.566)
Smoking			
Yes (Including Smoker or Former)	39/174	88/181	0.37 (0.252, 0.539)
No	8/28	9/21	0.52 (0.193, 1.358)

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PRESENTED BY: Shun Lu. Perioperative toripalimab + platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer : Interim event-free survival analysis of the phase III Neotorch study

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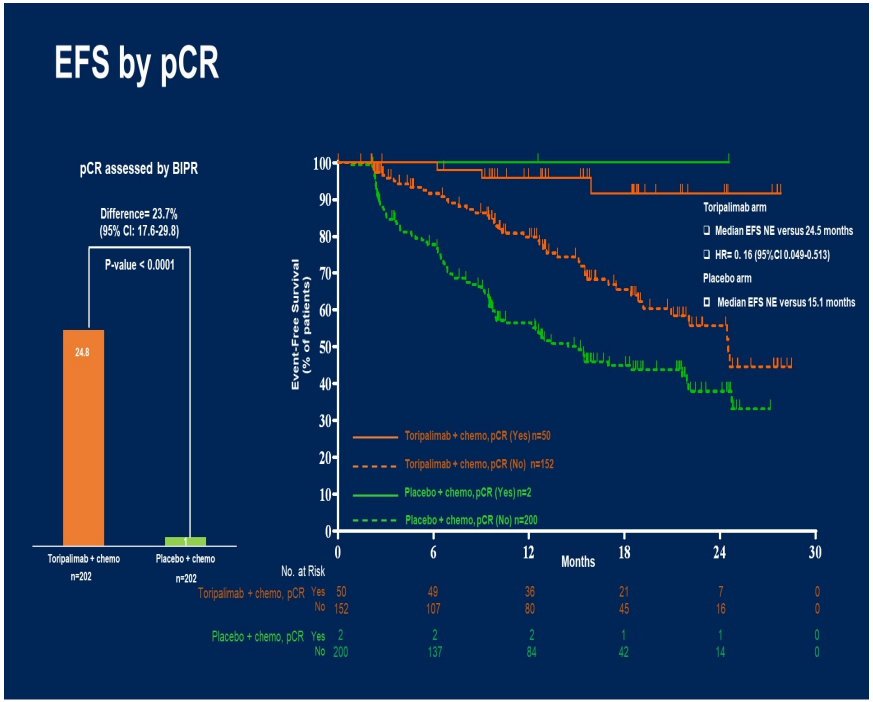
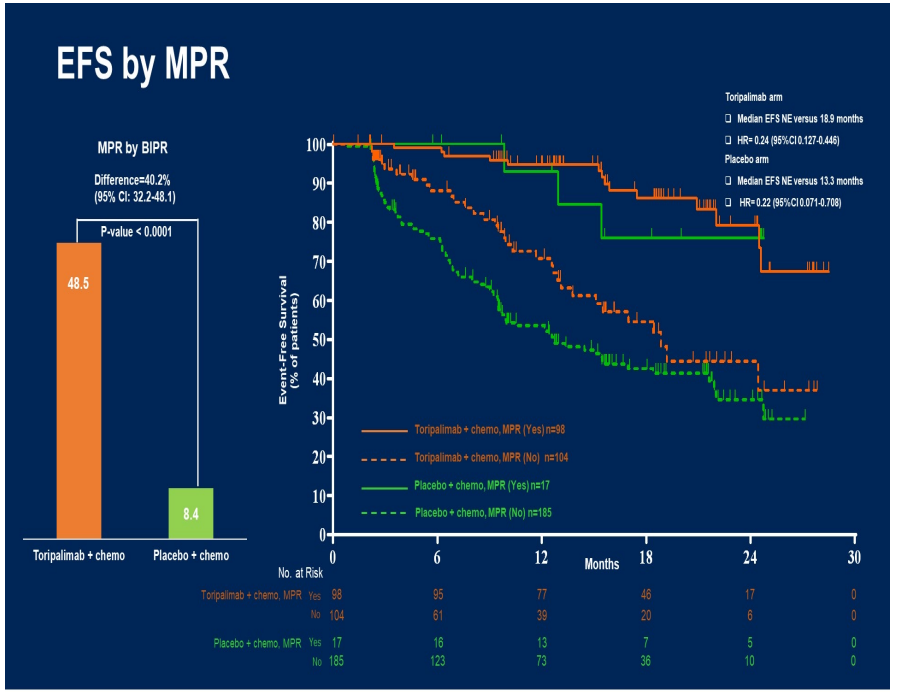
EFS for Stage III Patients Across Trials

Study	Stage IIIA	Stage IIIB
NEOTORCH	N=272 HR 0.44 (0.287-0.661)	N=129 HR 0.30 (0.149-0.559)
AEGEAN	N=338 HR 0.57 (0.39-0.82)	N=186 HR 0.83 (0.52-1.32)
KN 671	N=442 HR 0.54 (0.41-0.72)	N=126 HR 0.52 (0.31-0.88)
CM 816	N=228 HR 0.54 (~0.4-0.9)	NA
NADIM II Phase II	N=86 HR 0.47 (0.25-0.88)	No patients enrolled

Provencio M, et al. NEJM 2023

NEOTORCH (STAGE III)





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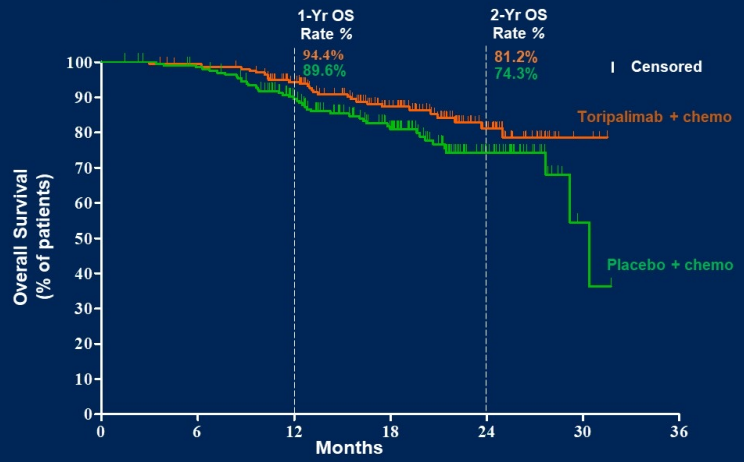
NEOTORCH (STAGE III) - EFS

Overall Survival Analysis

Median follow-up: 18.25 months
Intent-to-treat Stage III patients



No. at Risk

Toripalimab + chemo	202	198	169	107	45	3	0
Placebo + chemo	202	194	156	101	37	3	0

	No. of Events/ No. of Patients	Median OS *mo* (95% CI)
Toripalimab + chemo	28/202	NE (NE, NE)
Placebo + chemo	48/202	30.4 (29.2, NE)

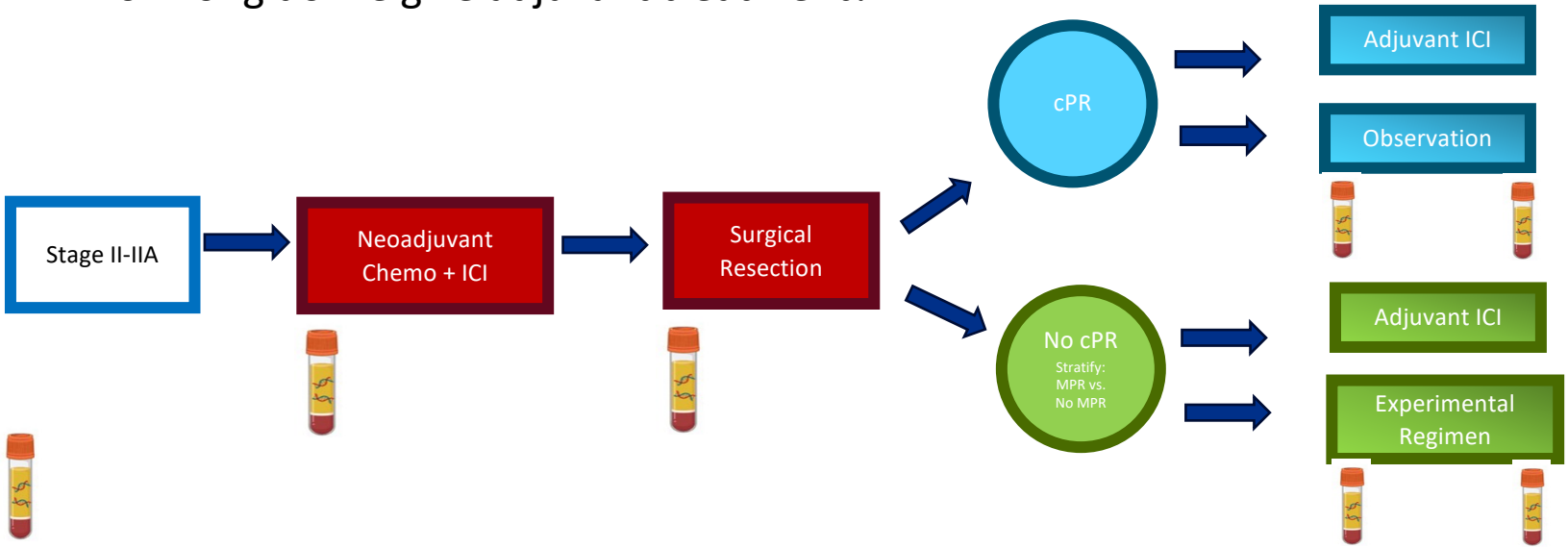
HR=0.62 (95% CI 0.38-0.999)

P=0.0502

Data cutoff date: Nov. 30, 2022
NE: not evaluable
HR; Hazard ratio
CI: confidence interval

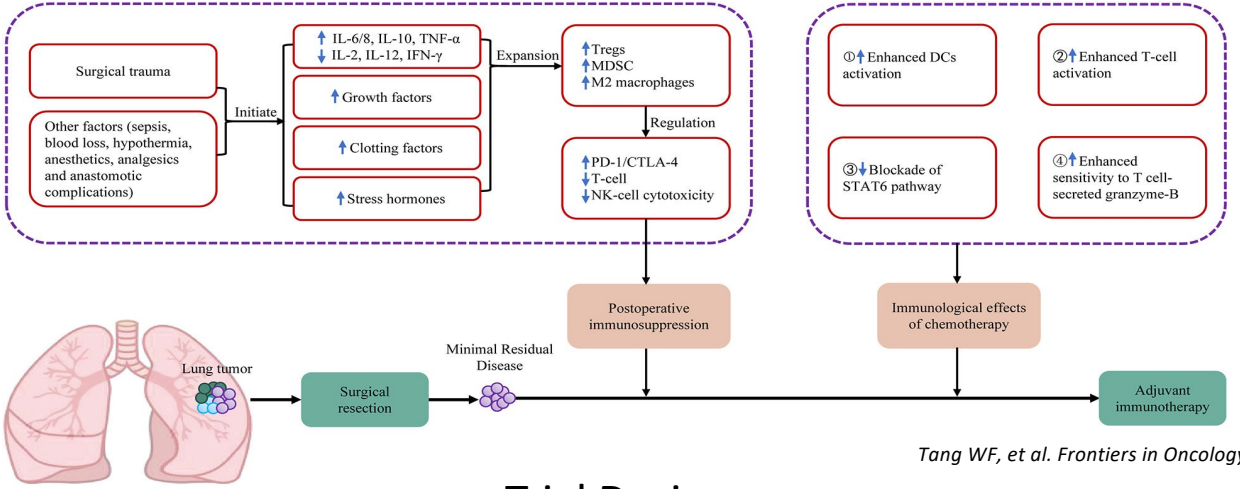
Key Questions

1. Do patients with a cPR need adjuvant treatment?
2. Are there subgroups of patients without a cPR who don't need adjuvant treatment?
3. Is it time to conduct a biomarker driven trial?
4. How long do we give adjuvant treatment?



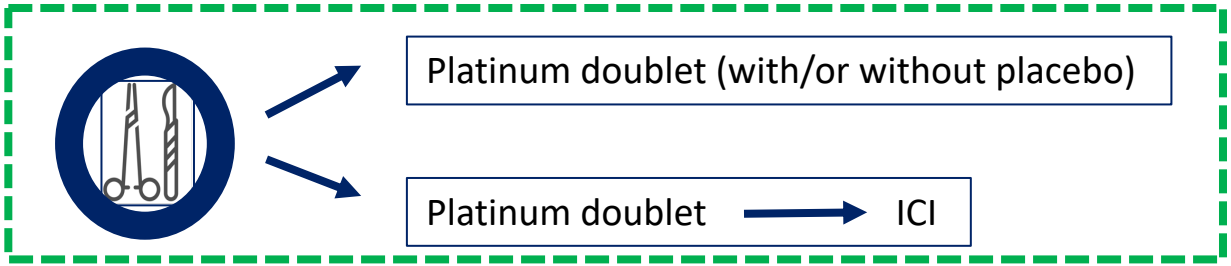
Adjuvant Phase III Trials – Trial Characteristics

Immunosuppressive Effects of Surgery and Chemotherapy



Tang WF, et al. Frontiers in Oncology 2023

Trial Design



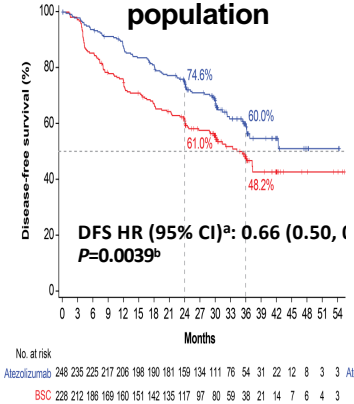
Adjuvant Phase III Trials – Trial Characteristics

Study	N	Stage	PD-L Testing requirement and Stratification	Allowance of EGFR/ALK+ Tumors	Primary Endpoint	Comments
IMpower 010 (NCT02486718) **Atezolizumb** **[Felip Lancet 2021; WCLC 2022)]**	1005	Resected stage IB (≥4 cm) to IIIA (AJCC 7th edition)	Required Stratification: <1% vs ≥1% 1-49% vs ≥50%	Allowed	DFS in a hierarchically design 1) Stage II-III pts with ≥ 1% PD-L1; 2) all Stage II-III pts; 3) ITT population	
KEYNOTE-091/PEARLS (NCT02504372) **Pembrolizumab** **[O'Brien Lancet Oncol 2022]**	1177	Resected stage IB (≥4 cm) to IIIA (AJCC 7th edition)	Required Stratification: <1% vs 1-49% vs ≥50%	Allowed	DFS overall population DFS pts with ≥ 50% PD-L1 expression	
NADIM-ADJUVANT **NCT04564157]** **Nivolumab**	210	Resected stage IB (=4 cm) to IIIA (AJCC 8th edition)	Not reported	Excluded	DFS	Accruing 6 cycles Nivo
ALCHEMIST/ANVIL **[NCT02595944]** **Nivolumab**	903	Resected stage IB (≥4 cm) to IIIA (AJCC 7th edition)	Required Stratification: <1% vs ≥ 1%	Excluded	OS	Results pending
BR31/IFCT1401 **NCT02273375]** **Durvalumab**	1415	Resected stage IB (≥4 cm) to IIIA (AJCC 7th edition)	Required Stratification: <1% vs 1-25% vs ≥25%	Allowed	DFS in patients with PD-L1 TC ≥ 25% and ≥ 1% DFS in all patients	Accruing

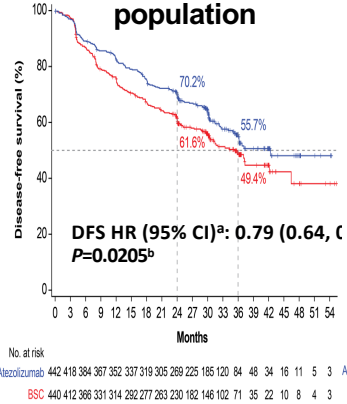
IMpower 010 and PEARLS/KEYNOTE 091 Primary DFS Endpoints

IMpower 010

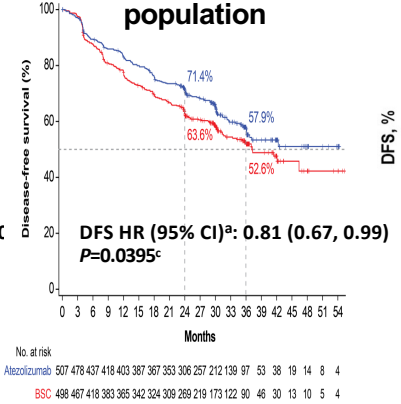
DFS: PD-L1 TC ≥1% stage II-IIIA population



DFS: All-randomised stage II-IIIA population

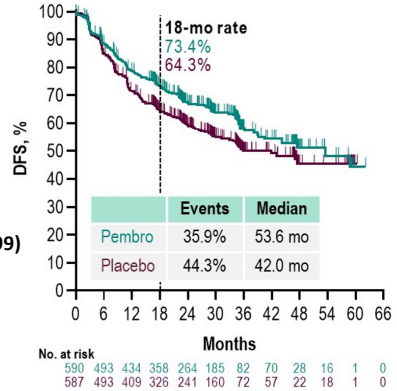


DFS: ITT (randomised stage IB-IIIA) population

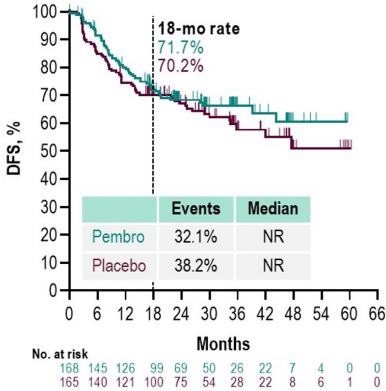


KN091

DFS, Overall Population
HR 0.76 (95% CI 0.63-0.91)
***P* = 0.0014**



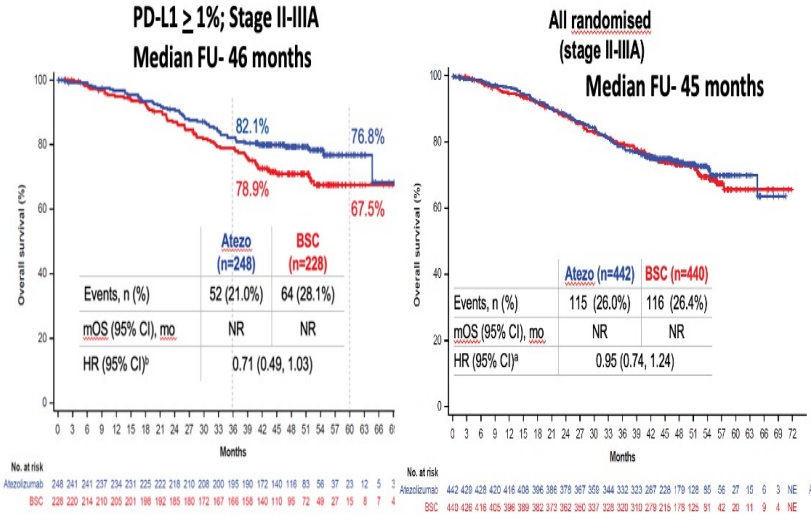
DFS, PD-L1 TPS ≥50% Population
HR 0.82 (95% CI 0.57-1.18)
***P* = 0.14**



IMMATURE

IMpower 010 and PEARLS/KEYNOTE 091 Overall Survival

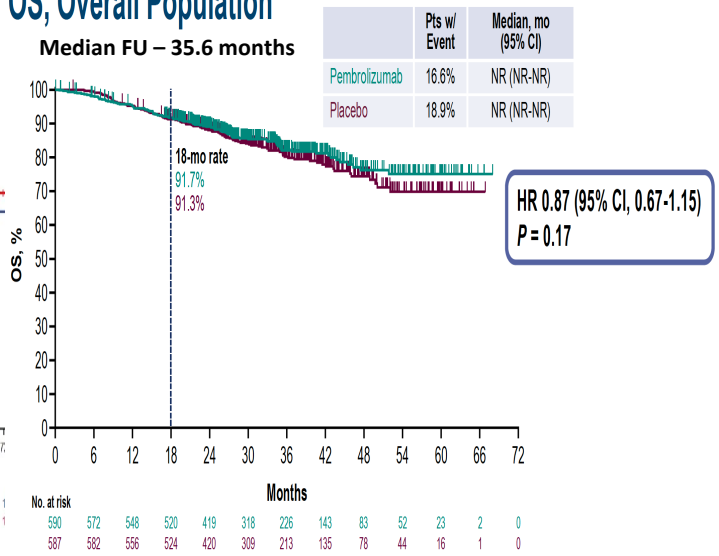
IMpower 010



*not formally tested

Felip E, et al. WCLC 2022

KN091



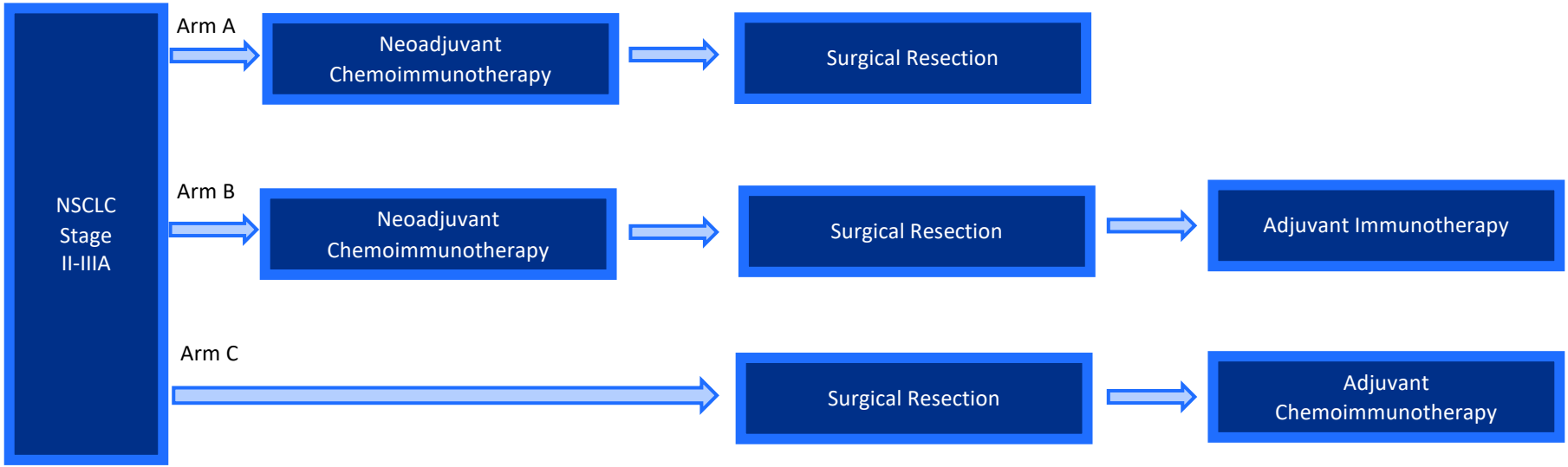
Paz-Ares K,, et al. Virtual ESMO Plenary 2022

By the Numbers

Trial	N	Follow Up	Stage III	PD-L1 ≥ 50% ≤ 1%	EFS HR (95% CI)	OS HR (95% CI)	Completed Neoadjuvant Tx	cPR	R0 Resection	Completed Adjuvant Tx
CM 816	358	41.4 months	66% (no IIIB) 7th ed	22% 43%	HR 0.68 (0.49-0.93)	HR 0.62 (0.36-1.05)	93.8%	24%	83.2%	NA
KN 671	797	25.2 months	70%	33% 36%	HR 0.58 (0.46-0.72)	HR 0.71 (0.54-0.99)	74.5%	18.1%	92%	40.4%*
AEGEAN	740	11.7 months	71%	29% 33%	HR 0.68 (0.53-0.88)	NR	84.7%	17.2%	94.7%	24.0%**
KN 091	1177	32.8 months	28.8%	28% 39%	HR 0.76 (0.63-0.91)	HR 0.87 (0.67-1.15)	-	-	-	51.7%

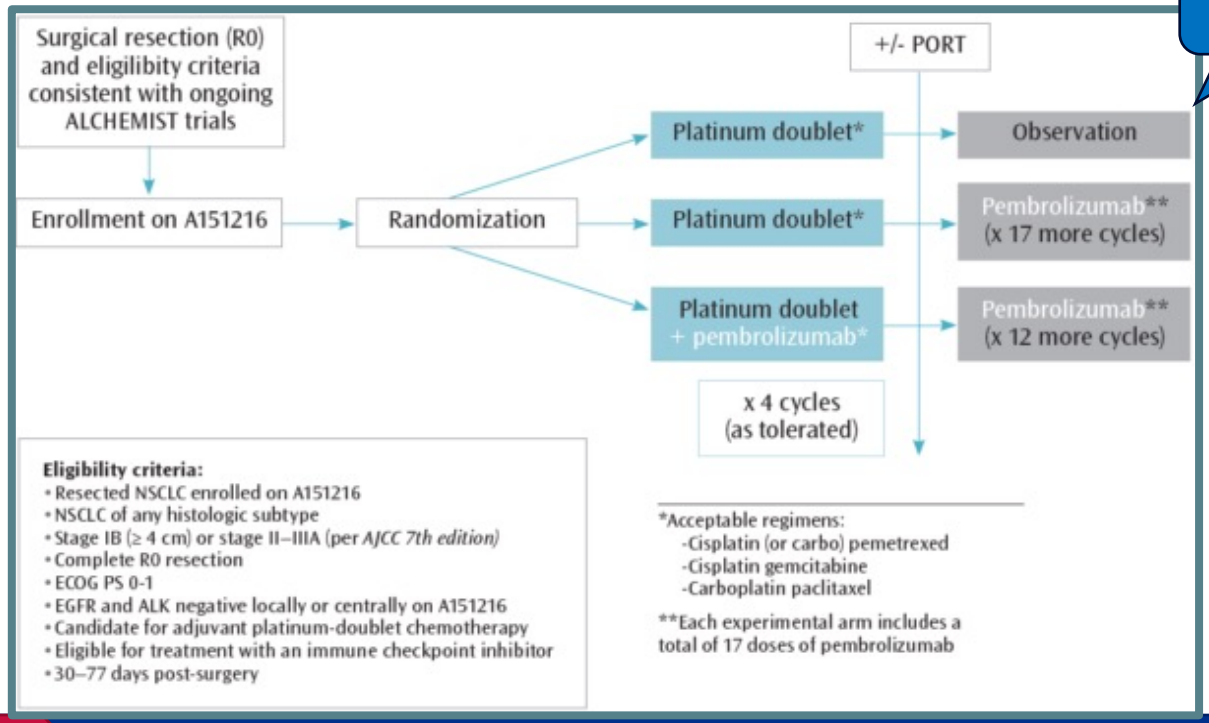
Different groups of patients went on neoadjuvant versus adjuvant trials.

Optimal Treatment Would Need a Clinical Trial



Next Steps:
Concurrent Chemotherapy + ICI VS Sequential Chemotherapy followed by ICI

ALCHEMIST: A081801



Next Steps: Minimal Residual Disease

MERMAID 1

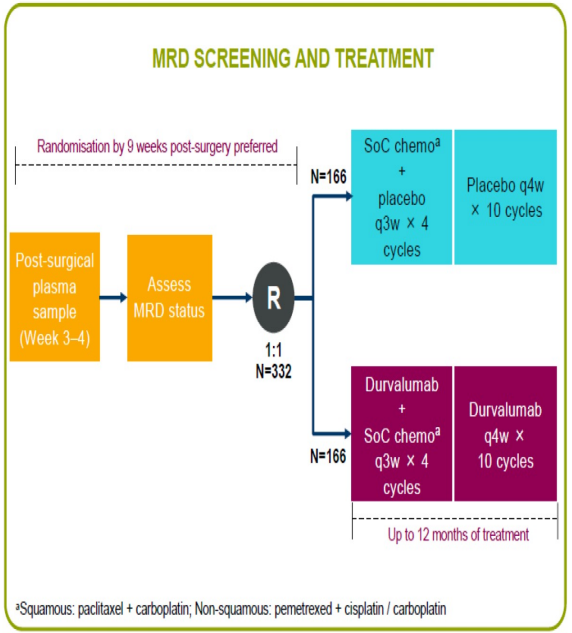
POPULATION

Inclusion:
- Stage II–III (including N2) completely resected NSCLC
- Collection of surgical specimen and whole blood
- PORT therapy is allowed
- **WES and development of personalised MRD panel**

Exclusion:
- EGFR / ALK mutations
- Received any adjuvant therapy
- Measurable disease

Stratification factors:
- Stage II vs III
- MRD+ vs MRD-
- PD-L1 (TC <1% vs TC ≥1%)

Screening: N=2225
Prevalence of MRD+: ~12%



ENDPOINTS

Primary:
- Disease-free survival in MRD+ patients

Selected secondary:
- Disease-free survival in full analysis set
- Disease-free survival by blinded independent central review
- Overall survival in MRD+ and full analysis set
- Safety and tolerability
- Patient-reported outcomes

Selected exploratory
- Progression-free survival / time to first subsequent therapy / time to second subsequent therapy

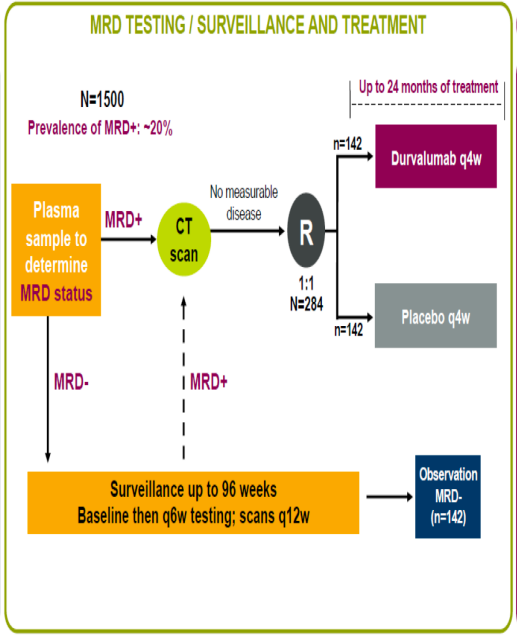
MERMAID 2

POPULATION

Inclusion:
- Stage II–III NSCLC completely resected
- Completed curative-intent therapy
- PORT is allowed
- **WES and development of personalised MRD panel**

Exclusion:
- EGFR / ALK mutations
- Evidence of measurable disease
- Adjuvant IO treatment
- Prior durvalumab

Stratification factors:
- PD-L1 (TC <1% vs TC ≥1%)
- Time to MRD emergence (≤6 months vs >6 months)
- Prior neoadjuvant immunotherapy (Yes vs No).



ENDPOINTS

Primary:
- DFS in PD-L1 TC ≥1%

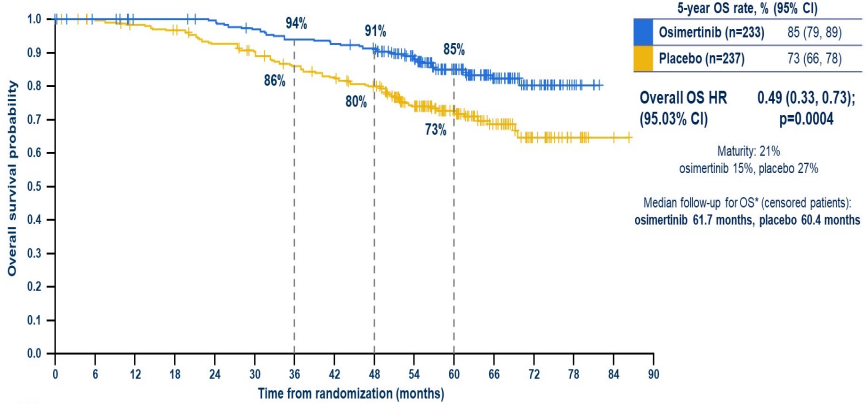
Selected secondary:
- DFS in full analysis set
- DFS by BICR in PD-L1 TC ≥1% and full analysis set
- PFS / time to first subsequent therapy / time to second subsequent therapy
- OS in PD-L1-TC ≥1% and full analysis set
- Safety and tolerability of durvalumab
- Patient-reported outcomes

Not actively accruing

ADAURA – Adjuvant Osimertinib

Overall survival: patients with stage II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the primary population of stage II–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)

Overall OS HR (95.03% CI) 0.49 (0.33, 0.73); p=0.0004

Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months

Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 59.9 months, placebo 56.2 months.

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CI, confidence interval; HR, hazard ratio; OS, overall survival

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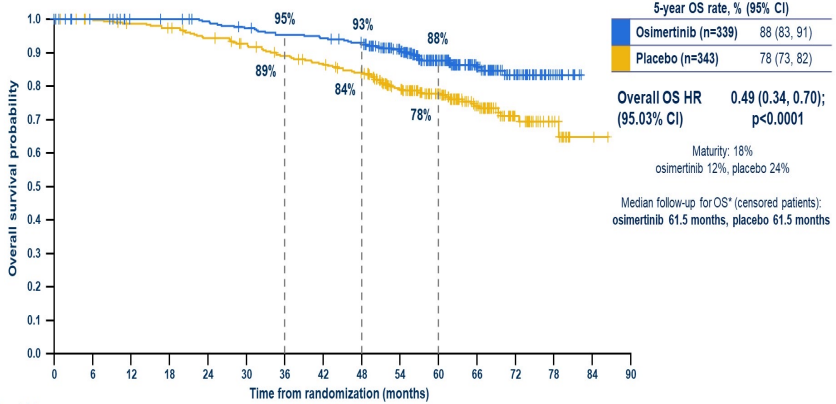
Overall survival: patients with stage IB / II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the overall population of stage IB–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) 0.49 (0.34, 0.70); p<0.0001

Maturity: 18%
osimertinib 12%, placebo 24%

Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.

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CI, confidence interval; HR, hazard ratio; OS, overall survival

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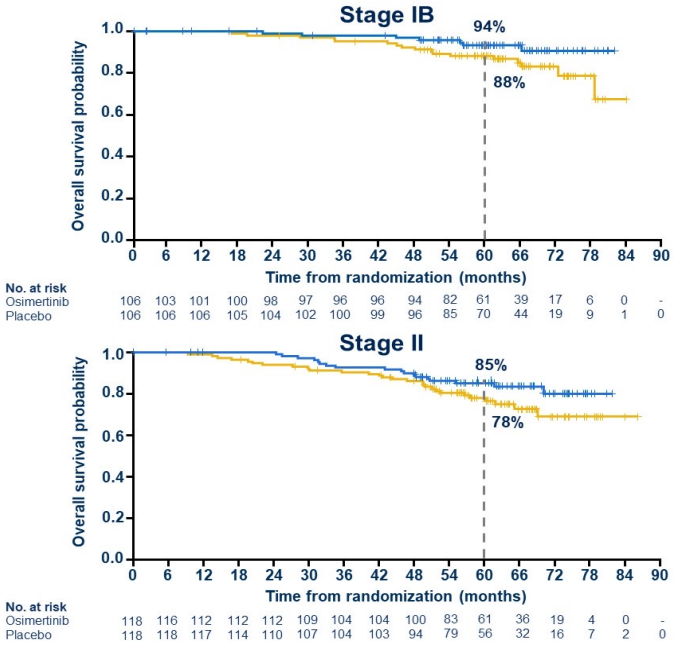
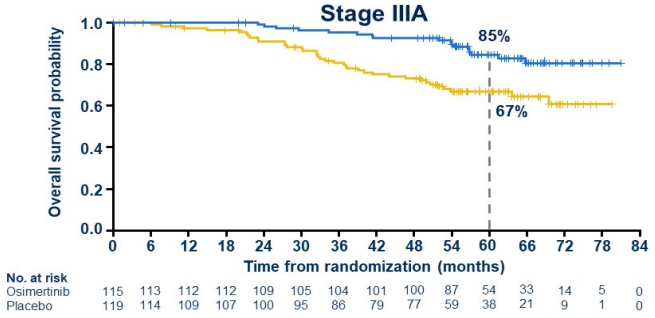
ADAURA – Adjuvant Osimertinib

Overall survival by disease stage



	Stage IB	Stage II	Stage IIIA
5 year OS rate, % (95% CI)			
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	**0.44 (0.17, 1.02)**	**0.63 (0.34, 1.12)**	**0.37 (0.20, 0.64)**



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Data cut-off: January 27, 2023. Tick marks indicate censored data.
CI, confidence interval; HR, hazard ratio; OS, overall survival

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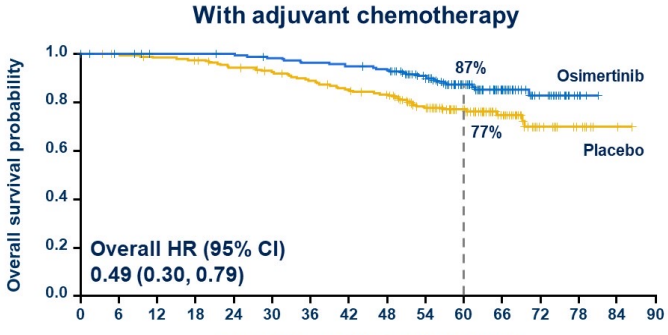
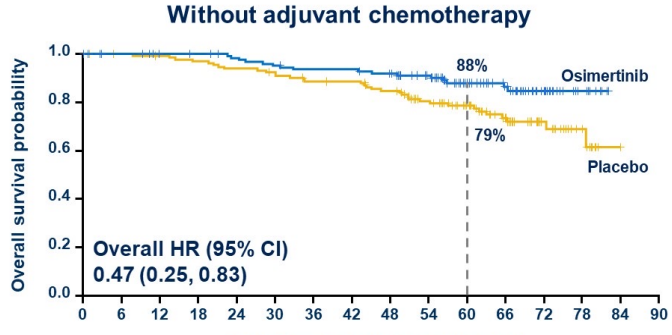
ADAURA – Adjuvant Osimertinib

OS in patients with and without adjuvant chemotherapy: patients with stage IB / II / IIIA disease



No. at risk

Osimertinib	203	200	197	197	196	192	188	185	182	155	104	58	25	7	0	-
Placebo	207	204	200	197	189	182	174	166	159	133	92	48	19	7	2	0



No. at risk

Osimertinib	136	132	128	127	123	119	116	116	112	97	72	50	25	8	0	-
Placebo	136	134	132	129	125	122	116	115	108	90	72	49	25	10	1	0

Data cut-off: January 27, 2023.
Overall population: stage IB / II / IIIA. Tick marks indicate censored data.
Use of adjuvant chemotherapy before randomization was allowed but not mandatory; decided by the physician and patient before enrollment.

CI, confidence interval; HR, hazard ratio; OS, overall survival

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Key Questions

1. When did post Osimertinib progression occur?
2. What are the characteristics of the patients who progress?
3. What were the sites of recurrence?
4. What does the Freedom From Brain Metastases curve show?
5. Can these results apply to patients whose tumors have other oncogenic drivers (ALK, ROS-1, RET, MET. HER2. NTRK)?
6. What about a neoadjuvant approach?

Ongoing Adjuvant TKI Trials

EGFR M+	N	Design	Primary Endpoint
ALCHEMIST	410 pts Stage IB-IIIA	Erlotinib versus placebo x 2 yrs (after chemotherapy)	Overall survival
ADUARA 2	380 Stage IA2 and IA3	Phase III, randomized, controlled, multi-center, international, 2-arm trial of Osimertinib versus placebo	DFS
APEX	606 Stage II-IIIA	Phase III, randomized, open label multi-center, 3-arm trial of Almonertinib vs Almonertinib + Chemotherapy vs Chemotherapy	DFS
ALK +	**N**	**Design**	**Primary Endpoint**
ALCHEMIST	168 pts Stage IB-IIIA	Crizotinib versus observation x 2 yrs (after chemotherapy)	Overall Survival
ALINA	255 pts Stage IB–IIIA.	Alectinib versus chemotherapy	Disease free survival

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Phase II Trial of Neoadjuvant Osimertinib for Surgically Resectable *EGFR*-Mutated Non-Small Cell Lung cancer

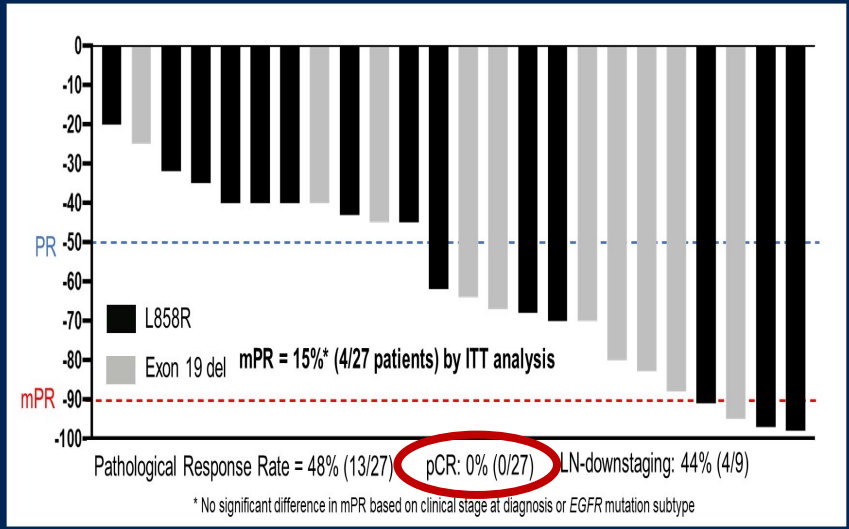
PI: Collin Blakely, MD, PhD, UCSF

Presented By: Jacqueline V. Aredo, MD, MS

University of California, San Francisco

USA

Primary Endpoint:
Major Pathologic Response Rate = 15%



Median duration of neoadjuvant osimertinib: 56 days (IQR 41-62)

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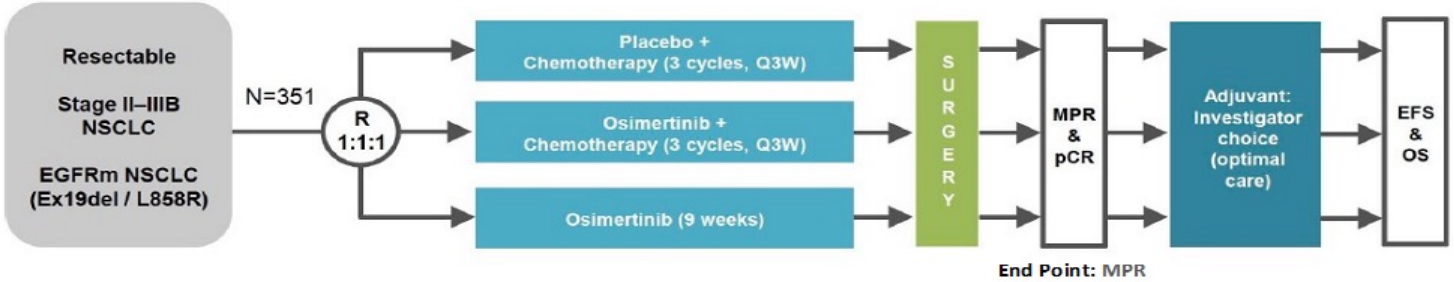
NEOADJUVANT APPROACH IN E*GFR* M+ EARLY NSCLC

NeoADAURA (NCT04351555): Phase III, Randomized, Controlled, Multicenter Study of Neoadjuvant Osimertinib in EGFRm Resectable NSCLC



Stratification:

- Stage II/III
- Non-Asian/Chinese/ other Asian
- Ex19del/L858R

Double-blind treatment arms:

1. Placebo QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2
2. Osimertinib 80 mg QD + investigator's choice of pemetrexed 500 mg/m^2 plus carboplatin AUC5 mg/ml.min or cisplatin 75 mg/m^2

Open-label (sponsor-blind) treatment arm:

3. Osimertinib 80 mg QD

Adjuvant therapy and follow-up:

- Patients will be followed up for OS until 5 years from surgery, with evaluation at 12 and 24 weeks post-surgery, then every 24 weeks, until disease recurrence or withdrawal of consent
- Osimertinib will be offered to all patients who complete surgery (+/- post-surgical chemotherapy) for up to 3 years or until disease recurrence

Tsuboi – WCLC 2020

Overall Summary

- Patients with resectable Stage II and III NSCLC have 3 options:
  a) Neoadjuvant chemo + ICI
  b) Adjuvant chemo followed by ICI
  c) Neoadjuvant chemo + ICI followed by post operative ICI (not yet FDA approved)

- All patients should be discussed in a multidisciplinary tumor board and a personalized treatment plan created.

- All patients should be tested for PD-L1, EGFR and ALK alterations (at a minimum).

- Patients with EGFR mutated tumors should receive adjuvant chemotherapy followed by Osimertinib.


Save The Date
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Singapore
September 9-12, 2023